Modeling Combinatorial Complexity in Cell Signaling

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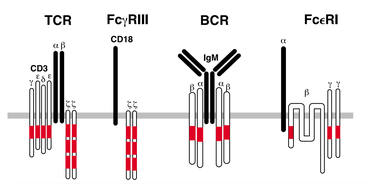
What is combinatorial complexity?

The number of molecular species that can arise in a model of signal transduction grows combinatorially with the number of signaling molecules and modification sites.

A protein with n phosphorylation sites has 2^n possible states.

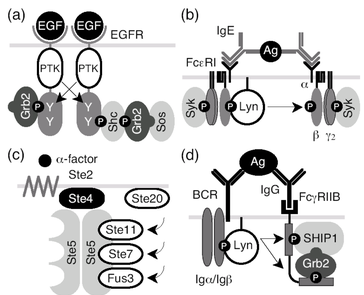
Multi-subunit immune receptors



Receptor	ITAMs	States of phosphorylation in an aggregate of two receptors
TCR	10	$2^{40} \sim 1.1\text{x}10^{12}$
FcγRIII	6	$2^{24} \sim 1.7\text{x}10^{7}$
BCR	4	$2^{16} = 65536$
FcεRI	3	$2^{12} = 4096$

Many signals are initiated through aggregation of receptors

Signaling involves formation of multi-component complexes



Protein-protein interactions amplify the number of states

Most states are tacitly omitted with common modeling approaches

How do we develop models that account for combinatorial complexity?

What effects arise from combinatorial complexity?

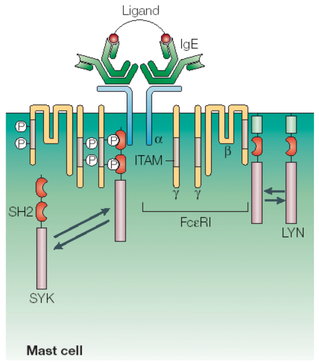
What is the effect of omitting large numbers of states?

Our approach

Assume only components directly involved in a particular chemical transformation affect the rate unless there is evidence to the contrary.

A handful of components, rules, and associated parameters give rise chemical networks with a large number of species and reactions.

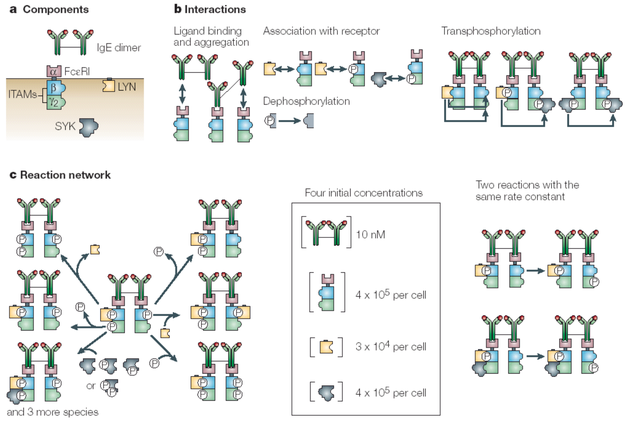
A model for proximal events in FcεRI signaling



Reaction network

- **354 species and 3680 reactions**

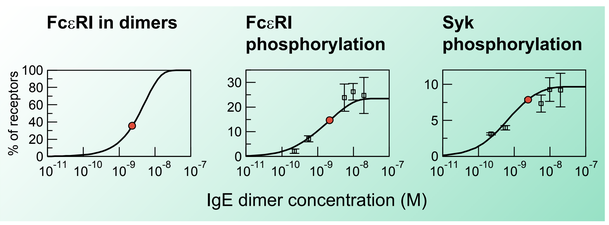
4 components / 7 domains / 9 interactions



A small number of parameters define the network

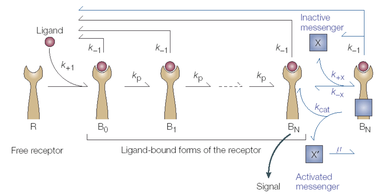
- 4 initial concentrations
- 21 rate constants

Comparison with experiment



Receptor and Syk phosphorylation saturate before aggregation
Lyn is limiting, but Syk is not (verified experimentally).

Kinetic proofreading of ligand-receptor interactions



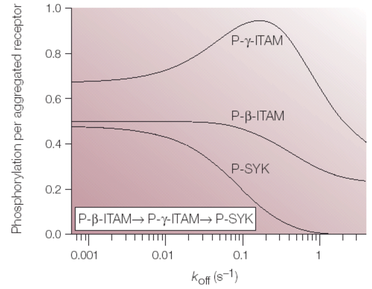
To initiate a signal, a ligand must remain bound long enough for phosphorylation and complex formation to occur.

Signal undergoes "proofreading" if dwell time of ligand is shorter than this time.

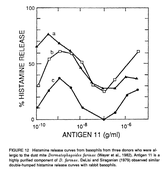
Testable effects of proofreading and ligand-receptor interactions

Detailed model predicts complicated dependence of phosphorylation levels on the off-rate.

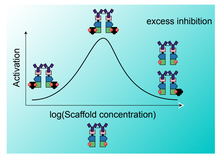
Bulk of proofreading occurs between receptor phosphorylation and Syk activation



Bimodal antigen dose-response curves: A multivalent scaffold effect?

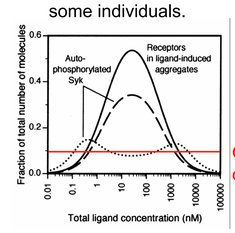


Optimal signaling at intermdiate scaffold concentration



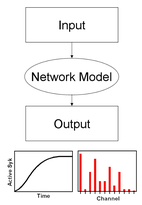
Bray and Lay, 1997; Burrack and Shaw, 2000; Levchenko et al., 2000.

Variations in Lyn and Syk levels could explain bimodal reponse of some individuals.



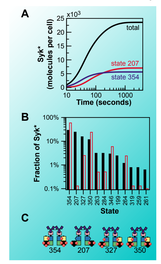
Optimal aggregate concentration

Restriction of network flows

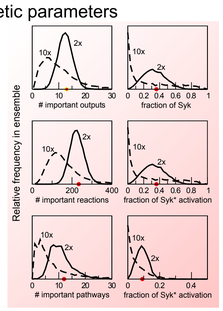


164 species contain Syk*

A small number of states contain most of the activated Syk (Syk*)



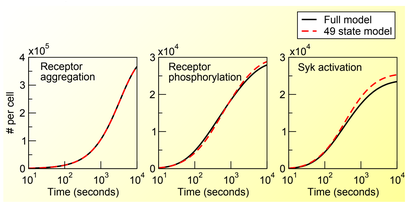
Robustness of flow restriction is tested by creating parameter set ensembles where parameters are varied by random amounts. Each parameter is varied by an amount x^p, p is random number [0,1] and x=2 or 10.



Prevalent states, reactions and pathways are determined by component concentrations and kinetic parameters

Model reduction

Simulated annealing finds networks with 50-80 species that reproduce main observables of full model.



49-state model reproduces network dynamics of full model with default parameters.

Error of reduced models is measured by the RMS error of six observables (FcεRIβ phosphorylation, FcεRIγ phosphorylation, Syk linker phosphorylation, Syk activation loop phosphorylation, constitutive Lyn association, and Lyn recruitment) at three time points (t=10, 100, and 1000 seconds), based on comparison with the full model.

Optimization is performed by random removal of nodes from the reaction network. A move is accepted if the error of the new model falls below a threshold. A node is added after a series of failed moves. The 49 state model was obtained with a threshold of 10%. Default parameter values are used in the optimization.

Reduced models do not accurately predict dynamics in parameter set ensembles.

49 state model (118 reactions)

	Default set	2x ensemble	10x ensemble
Mean relative error	6.5%	37%	301%
% sets error <10%	–	4.6%	0.1%
% sets error >50%	–	26%	83%

81 state model (248 reactions)

	Default set	2x ensemble	10x ensemble
Mean relative error	4.3%	32%	89%
% sets error <10%	–	15%	1.5%
% sets error >50%	–	20%	66%

Full model is required to predict dynamics across a wide range of operating conditions.